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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/463,733		CHARLES ZUKER	02307E-085110US	6739

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EXAMINER	
MYERS, CARLA J	
ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 11/18/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/463,733	ZUKER, CHARLES	
	Examiner	Art Unit	
	Carla Myers	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 August 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-17,19,20 and 22-38* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 3-17, 19, 20, 22-38* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

1. This action is in response to the amendment filed August 27, 2002. Applicants amendments and arguments have been thoroughly reviewed but are not persuasive to overcome all grounds of rejections. All rejections not reiterated herein are hereby withdrawn. This action is made final.

2. Claims 1, 2-17, 19, 20, and 22-38 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to methods for screening for modulators of RDGC GPCR phosphatase activity, wherein the method comprises assaying for a compound which modulates the activity of an RDGC phosphatase. The specification (page 8) broadly defines a RDGC phosphatase as including polymorphic variants, alleles, mutants, and closely related interspecies variants that have at least 60% identity at the amino acid level to a RDGC phosphatase and which have GPCR phosphatase activity. Applicants cite Steele et al (Cell (1992) 69:669-676) as teaching an example of an RDGC protein. In particular, Steele teaches the sequence of Drosophila retinal degeneration C (RDGC) protein. While the prior art has defined a single RDGC protein by its structural formula, the specification has not provided an adequate written description of and has not conveyed that at the time of filing applicants were in possession of a representative number of the claimed protein molecules. The specification has not disclosed any non-drosophila RDGC proteins, nor has the specification disclosed any allelic variants or any mutants having functional activities similar to RDGC. While it is noted that the claims are

limited to proteins having RDGC phosphatase activity, this functional limitation is so broad so as to not impart any meaningful limitation since proteins having phosphatase activity or having GPCR phosphatase activity represent a general, non-specific class of proteins. The general knowledge in the art concerning alleles does not provide any indication of how the structure of one allele is representative of unknown alleles. Moreover, the structure and function of one molecule does not provide guidance as to the structure and function of other molecules. Therefore, the description of one molecule encoding a protein having the functional activities characteristic of wild-type RDGC is not representative of a genus of allelic variants, mutants and homologs having RDGC phosphatase activity. It is noted that the claims themselves do not recite any structural properties for the claimed proteins. *Vas-Cath Inc. V. Mahurkar*, 19 USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed". Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. 112 is severable from its enablement provision. In *The Regents of the University of California v. Eli Lilly* (43 USPQ2d 1398-1412), the court held that while Applicants are not required to disclose every species encompassed by a genus, the description of a genus is achieved by the recitation of a representative number of DNA molecules, usually defined by a nucleotide sequence, falling within the scope of the claimed genus. At section B(1), the court states that "An adequate written description of a DNA...'requires a precise definition, such as by structure, formula,

chemical name, or physical properties', not a mere wish or plan for obtaining the claimed chemical invention". The limited information provided in the specification is not deemed sufficient to reasonably convey to one of skill in the art that Applicants were in possession of a representative number of allelic variants, mutants and homologs having the ability to dephosphorylate any GPCR. Therefore, the written description requirement has not been satisfied for the claims as they are broadly written. Applicants attention is drawn to the Guidelines for the Examination of Patent Applications under 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

Response to arguments:

In the response filed August 27, 2002, Applicants traversed this rejection by stating that "in light of the disclosure of the specification, taken together with that which is known in the art, the genus of RDGC phosphatases for use in the invention are defined by a structural feature that is a hallmark of the genus." This argument is not convincing because the claims do not recite any structural features. It is unclear as to what structural feature Applicant is referring to as being a hallmark of the genus. The prior art teaches a single Drosophila RDGC nucleic acid. However, the present claims are drawn to any RDGC nucleic acid. As defined in the specification (page 8), a RDGC phosphatase is intended to include all polymorphic variants, alleles, mutants, and closely related interspecies variants that have at least 60% identity at the amino acid level to a RDGC phosphatase and which have GPCR phosphatase activity. The

specification and art do not teach any such polymorphic variants, alleles, mutants, or closely related interspecies variants. The fact that the specification states that RDGC phosphatases include molecules having 60% identity to a reference sequence is not equivalent to including a limitation in the claims stating that the RDGC phosphatase has at least 60% identity to a reference molecule. The teachings in the prior art of a single Drosophila RDGC nucleic acid does not place applicants in possession of all possible variants of this nucleic acid and protein. Applicants have not established that at the time of the invention that they were in possession of a representative number of RDGC phosphatases within the very broadly claimed genus of any RDGC phosphatases.

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 2-17, 19, 20, and 22-38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Byk in view of Zuker (reference "AG") and Zuker (GenBank Accession No. M17718; reference "AE").

Byk teaches a method of screening *in vitro* for compounds which modulate RDGC activity. Specifically, Byk teaches a method comprising providing a first sample of eye membranes containing wild-type RDGC and a second sample of eye membranes containing

mutant RDGC; contacting the sample with a compound (such as calcium or arrestin) which is suspected of having the ability to modulate RDGC GPCR phosphatase activity, and detecting RDGC GPCR phosphatase activity by means of a phosphorylation assay that is conducted by measuring mobility on an electrophoretic gel (see figures 2 and 5, and page 1909). Byk teaches that the GPCR rhodopsin is a major substrate for RDGC phosphatase (page 1908) and specifically exemplifies methods which monitor calcium and arrestin for their ability to modulate dephosphorylation of rhodopsin by RDGC. Byk does not teach performing a signal transduction assay to detect phosphatase activity, does not teach applying the screening method to one performed *in vivo*, and does not teach the use of recombinant RDGC or recombinant GPCR.

Zuker teaches a method of measuring membrane potential changes in intact *Drosophila* photoreceptor cells and calcium changes in *Drosophila* transgenic for a particular rhodopsin (Figure 4). At page 575, Zuker states that "the genetic dissection of this [phototransduction] pathway in humans and flies has provided fundamental insight into the molecular and cellular basis of inherited retinal disorders". Zuker (page 575) further states that "It is here where the study of phototransduction in *Drosophila* offers unprecedented versatility. The study of this signal cascade in the fruit fly *Drosophila melanogaster* makes it possible to use powerful molecular genetic techniques to identify novel transduction molecules and then to examine the function of these molecules *in vivo*, in their normal cellular and organismal environment". Furthermore, Zuker (GenBank Accession No. M17718) teaches the isolated nucleic acid

sequence of *Drosophila* RDGC, which can be used for synthesizing recombinant RDGC and for generating transgenics expressing RDGC.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Byk so as to have used recombinant RDGC and rhodopsin in place of native RDGC and rhodopsin since nucleic acids encoding these proteins were well known in the art at the time the invention was made and the use of nucleic acids to encode recombinant proteins was conventional in the art and because Zuker exemplifies transgenic *Drosophila* which express recombinant rhodopsin. Furthermore, it would have been obvious to one of ordinary skill in the art to have transformed isolated cells, particularly insect cells, with expression vectors comprising rhodopsin and RDGC nucleic acids since Byk teaches that rhodopsin and RDGC proteins are involved in the phototransduction signal cascade and because this would have achieved the advantage of using an isolated system in which the presence of a particular pathway component could be controlled and the expressed proteins would be in an environment similar to the normal cellular environment (i.e., in an insect cell). It is noted that Zuker teaches the advantages of the ability to dissect pathways molecularly. To most closely mimic a natural environment, it would have been desirable and obvious to one of ordinary skill in the art at the time the invention was made to have used whole cells and transgenic organisms in the method of Byk instead of membrane preparations because Zuker teaches that light and calcium applied to whole cells can be used as methods of screening for compounds which influence the phototransduction pathway (see, for example, Figure 3) and

Zuker teaches the importance of assaying molecular mechanisms *in vivo* in their normal cellular and organismal environment.

With respect to claims 37 and 38, Byk does not specifically teach packaging RDGC, GPCR and instructions in a kit. However, reagent kits for performing diagnostic methods were conventional in the field of molecular biology at the time the invention was made. Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have packaged the RDGC and a GPCR in a kit for the expected benefits of convenience and cost-effectiveness for practioners in the art wishing to assay for RDGC phosphatase activity or wishing to assay for compounds which modulate RDGC phosphatase activity. Furthermore, it is noted that the written material in the instructions is not considered to be within the statutory classes and does not carry patentable weight (see MPEP 706.03(a)). However, it would have been further obvious to one of ordinary skill in the art at the time the invention was made to have included instructions in the kit in view of the conventionality of including instructions in kits for facilitating the use of the packaged reagents.

Response to arguments:

In the response filed August 27, 2002, Applicants traversed this rejection by stating that Byk does not "teach an *in vivo* analysis that establishes the direct role of RDGC phosphatase in GPCR-mediated signal transduction." Accordingly, Applicants conclude that there is no suggestion in the prior art to use RDGC phosphatase as a target to modulate GPCR-mediated signal transduction.

Applicants arguments have been fully considered but are not persuasive because there is no requirement that one know the direct *in vivo* role of RDGC phosphatase in GPCR-mediated signal transduction in order to arrive at or perform the presently claimed invention. The claims do not require directly measuring or evaluating the effect of RDGC phosphatase on a particular step in the GPCR-signal transduction pathway. Rather, the claims require measuring a change in RDGC GPCR phosphatase activity as indicative of a modulator of G protein coupled receptor signal transduction. Byk (page 1908) teaches that phosphorylated rhodopsin is a major substrate for RDGC phosphatase. Byk (page 1910) also teaches that following phosphorylation of rhodopsin and release of arrestin, "p-R then becomes an efficient substrate for rhodopsin phosphatase, which safely reintroduces it to the rhodopsin pool, ready for the next round of photoexcitation." The reference further states (page 1910) that "(g)enetic analysis of the *Drosophila* mutant rdgC revealed that retinal degeneration is dependent on high levels of activated rhodopsin and placed the site of action of the *rdgC* gene product before phospholipase C." Additionally, Zuker (Figure 1) teaches the phototransduction pathway in *Drosophila* photoreceptors, including the step in which rhodopsin is dephosphorylated by RDGC phosphatase and the role of this step in the GPCR-mediated signal transduction pathway. Accordingly, the teachings of Byk and Zuker clearly establish that the dephosphorylation activity of RDGC is an essential step in the GPCR-mediate signal transduction pathway. Thereby, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have generated a method for identifying additional compounds which modulate

RDGC phosphatase activity as a means for identifying compounds which potentially effect GPCR-mediate signal transduction and thereby effect phototransduction. Furthermore, it is noted that claims 37 and 38 are drawn to kits comprising a G-protein coupled receptor, RDGC phosphatase and instructions. As discussed in the above rejection, the actual writing in the instructions does not carry patentable weight. The cited prior art teaches methods which screen for compounds that alter the ability of RDGC phosphatase to dephosphorylate the G-protein coupled receptor rhodopsin. The claims to the kits do not require knowledge of a direct *in vivo* role of RDGC phosphatase in GPCR-mediated signal transduction. Accordingly, Applicants arguments regarding claims 37 and 38 are not persuasive because the arguments are not directed to limitations recited in the claims.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Carla Myers whose telephone number is (703) 308-2199. The examiner can normally be reached on Monday-Thursday from 6:30 AM-5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones, can be reached on (703)-308-1152. The fax number for the Technology Center is (703)-305-3014 or (703)-305-4242.

Any inquiry of a general nature or relating to the status of this application should be directed to the receptionist whose telephone number is (703) 308-0196.

Carla Myers

November 14, 2002

CARLA J. MYERS
PRIMARY EXAMINER